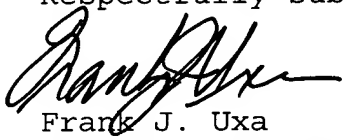
REMARKS

The amendments have been made to correct minor typographical errors and to provide that the specification reads more consistently. No new matter has been added.

Respectfully submitted,



Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (949) 450-1764

FJUxa/ac

Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The third paragraph on page 1 has been amended as follows:

--Although the term "enhancement of pharmacokinetic disposition" as used herein, may mean an enhancement in permeability, an enhancement of pharmacokinetic disposition may also mean an enhancement in, for example, bioavailablity, [sequenstration] sequestration and release characteristics of the agonists.--

The last paragraph beginning on page 2 has been amended as follows:

--Still further in accordance with the invention, agonists employed in the present compositions include those compounds, mixtures of compounds, mixtures of other materials, which are useful to provide a therapeutic benefit or effect when administered to a patient, e.g. a human patient. The agonists useful in this invention include imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist includes quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline (hereinafter ["bromonidine"] "brimonidine"), biologically compatible salts thereof and esters thereof.--

The first full paragraph on page 8 has been amended as follows:

--In one useful embodiment, the amount of agonist in the present composition is in the range of about 0.05% to about 30% (w/v) or more of the composition. Preferably, the amount of agonist is in the range of about 0.1% (w/v) to about 10% (w/v). More preferably, the amount of agonist is in the range of about 0.1% (w/v) to about 0.6% (w/v). Even more preferably, the agonist is [bromonidine] brimonidine and is present in the composition in the range of about 0.1% (w/v) to about 0.6% (w/v), preferably about 0.13%.--

The last paragraph beginning on page 9 has been amended as follows:

--In one embodiment, a complex of an agonist and a FAC may exist as a salt outside of a solution. For example, a complex of brimonidine and linoleic acid may be a powder. Furthermore, this complex may be added to a solution, for example a saline solution. Preferably, the agonist and the FAC still remain as a complex. In one embodiment, the solution containing the complex, for example a complex of [bromonidine] brimonidine and linoleic acid, is administered to the eye to treat glaucoma. In one embodiment, the complex remains intact at the site where the agonist may exert a therapeutic effect. In a preferred embodiment, the complex dissociates at or near the site where the alpha-2-adrenergic agonist may exert a therapeutic effect. For example, a complex of [bromonidine] brimonidine linolenic acid may dissociate to release [bromonidine] brimonidine at or near the ciliary body in the eye, wherein the [bromonidine] brimonidine can act on receptors located on the ciliary body to reduce the production of aqueous solutions, thereby treating glaucoma.--

The third full paragraph on page 11 has been amended as follows:

--In one embodiment, the complexation of agonists with FACs further help solubilize the agonists in solution and preferably reduces irritation when the agonists are administered to sensitive tissues. For example, an eye drop solution having a pH of about 7 may contain insoluble agonist ions, such as [bromonidine] brimonidine tartrate ions. If such a solution is administered to the eye, a sensitive tissue, the insoluble agonist ions may cause discomfort and irritation. However, a complex of agonist and FAC may help solubilize the agonist in such a solution. In a preferred embodiment, the solution containing a solubilized agonist results in less irritation as the solution is applied to a sensitive tissue, for example the eye. In a more preferred embodiment, the solution containing solubilized agonist results in little or no irritation when the solution is administered to a sensitive tissue.--

The first full paragraph on page 16 has been amended as follows:

--In order to insure that the pH of the liquid carrier component, and thus the pH of the composition, is maintained within the desired range, the liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as [CO .] CO. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.--

The sub-title on page 18, under Example 1, has been amended as follows:

--EXAMPLE 1

Effects of [bromonidine] brimonidine-linoleic acid on Intra Ocular Pressure--

The last paragraph on page 18, under Example 1, has been amended as follows:

--The data below shows the percent change with time of Intra Ocular Pressure (mm Hg) after an administration of [bromonidine] brimonidine-linoleic acid complex at time 0. The complex is an ion pair formulation of 0.131% [bromonidine] brimonidine and 0.126% linoleic acid.--

The first full paragraph on page 19, under Example 2, has been amended as follows:

--The relative sedative effects of [bromonidine] brimonidine-linoleic acid (compound 65) were compared to saline (compound 62) and Brimonidine tartrate (compound 60). This study involved cross overs and a one-week wash out in between the administration of the various compounds.--

On page 20, the step No. 8, under Example 2, has been amended as follows:

--8. The test compounds were coded: 62-Saline, 65-[bromonidine] brimonidine tartrate, 60-[bromonidine] brimonidine-linoleic acid.--

The second full paragraph on page 22, has been amended as follows:

--Half the monkeys given the test compound [bromonidine] brimonidine-linoleic showed low activity (1 hour post dose), with the exception of monkey #19. Monkey #19 did not appear to be sleepy, inactive or have heavy eyes and seemed to react similarly to all test compounds. She seems to be very comfortable in the chair, and when there were no distractions she tended to close her eyes and relax.--

The last paragraph on page 22, has been amended as follows:

--The dosing with [bromonidine] brimonidine-linoleic acid complex appears to cause more sedation in the monkeys than dosing with saline. In general when the monkeys were dosed with saline, they were quiet and easy to handle for all readings. However, dosing with [bromonidine] brimonidine tartrate causes more sedation than dosing with [bromonidine] brimonidine-linoleic acid. When the monkeys were dosed with [bromonidine] brimonidine tartrate, on average they became sleepy and inactive with heavy eyes. This observation was seen usually at the 2-hour time point and most of the animals remained this way through the end of observations.--

The first full paragraph on page 23, has been amended as follows:

--Without wishing to limit the invention to any mechanism or theory of operation, it is believed that one of the reasons that [bromonidine] brimonidine-linoleic acid complex causes less sedation than [bromonidine] brimonidine tartrate is that it partitions more in the lipid compartments. In other words, the [bromonidine] brimonidine-linoleic acid complex is more trapped in the lipid compartments, and is not as available to circulate in the blood stream to eventually travel to the brain to cause sedation.--

The sub-title on page 23, under Example 3, has been amended as follows:

--EXAMPLE 3

Effects of [bromonidine] brimonidine-linoleic acid ion pair complex (0.2%) on rabbit intraocular pressure--

The last paragraph on page 23, has been amended as follows:

--One group of animals (both sexes) was used per screening study. The test compound (20μL of 0.2% [bromonidine] brimonidine-linoleic acid ion pair complex) was administered to the surface of the cornea using an automatic pipette or an appropriate device.--

On page 25, the step No. 10, under Example 3, has been amended as follows:

--10. Place the pnematonometer tip on one eye at the [ ] site where the curvature of the cornea is greatest. Let the probe shank travel to the black line, not the red line. Persist until a stable reading with the standard deviation below 1.0 is obtained. Repeat the procedure for the contralateral eye. Record the data. (Note: If the animal is upset by the restraint, the reading will be artificially high and cannot be used. Use gentle restraint).--

On page 25, the step No. 11, under Example 3, has been amended as follows:

--11. At the end of the 0, 6, 24, 30, 48, 54, 72, 78 [ ] and 96 hour measurements, use an automatic pipette to apply 20μL of the test compound to the surface of the

cornea of one eye. After the 102 hour measurements, the eyes will be washed out with Refresh® and Prefrin®.--

The last paragraph on page 26, has been amended as follows:

--The effects of [bromonidine] brimonidine-linoleic acid ion pair complex are shown on Table 2. It appears that the complex is able to reduce intraocular pressure in a rabbit's eye for at least 6 hours. For example, 6 hours after the administration at times 0 hr, 24hr, 48hr, 72 hr, and 96 hr, the intraocular pressure remained below the initial time. However, it also appears that the effect of the complex is less than 18 hrs. For example, 18 hrs after administration of the complex at time 6 hr, the intraocular pressure returned to about the same initial level.--

On page 28, the sentence below the table, has been amended as follows:

--*[bromonidine] brimonidine-linoleic acid ion pairs were administered at these time points.--